May 13, 1999

VETERINARY SERVICES MEMORANDUM NO. 800.91

Subject: Categories of Inspection for Licensed Veterinary Biologics Establishments

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

The purpose of this memorandum is to provide a list of the categories which are used for in-depth inspections of licensed veterinary biologics establishments by inspectors of the Animal and Plant Health Inspection Service (APHIS) under the provisions of 9 CFR Part 115. Licensees should use this list of categories of inspection as an aid in understanding APHIS inspections and as a guide for self-inspections to determine their compliance with the Virus-Serum-Toxin Act (VSTA).

II. GENERAL

Regulations in 9 CFR Part 115 give authority for any USDA inspector to enter any establishment where any biological product is being prepared, at any hour during the day or night, and inspect without previous notification. APHIS does these unannounced inspections of licensed veterinary biologics establishments to determine whether products are being prepared in compliance with the VSTA and regulations. Internal guidelines have been developed for APHIS inspectors that list 14 categories of inspection for in-depth inspections, and what audits and observations may be made in each category. This list of categories is not necessarily all-inclusive, but may help the veterinary biologics industry to maintain compliance with the VSTA and regulations.

III. GUIDELINES

When inspecting licensed veterinary biologics establishments, APHIS inspectors should use the 14 categories of inspection described in this section to define inspection responsibilities and serve as a format for the inspection report. The checklist of audits and observations given for each inspection category should not be considered limiting or all-inclusive. Inspectors can inspect the entire premises of the establishment, including the following: all buildings, compartments, and other places; all biological products, and organisms and vectors in the establishment; all materials and equipment, such as chemicals, instruments, apparatus, and the like; and the methods used in the manufacture of, and any record pertaining to, the production, testing, disposition, sale, or distribution of veterinary biological products produced at each establishment.

Following is the list of inspection categories, with audits and observations for each, that APHIS inspectors may use for guidance when conducting inspections:

A. Licenses and Permits

1. *Audits* :

a. Compare the firm's U.S. Veterinary Biologics Establishment License with information on file at the Center for Veterinary Biologics (CVB). Review the ownership, parent company, and subsidiary and division relationships with the firm's official in charge. Verify addresses, locations, and other information on the license.

b. Discuss the activity of each licensed product with the official in charge. Be sure that conditional licenses have not expired. Confirm that the firm's file of U.S. Veterinary Biological Product Licenses matches information from CVB files.

c. If a product is not being produced, determine the last date of production (batching or similar date). The firm may wish to voluntarily return inactive product licenses to APHIS for termination. If the firm wishes to voluntarily return an inactive license or if a product has not been produced in over 5 years, report the situation to Licensing and Policy Development (LPD) for action.

d. For product licenses with restrictions, determine if the firm is following the restrictions.

e. Determine if the facility is approved for storing veterinary biological products imported under a U.S. Veterinary Biological Permit for Distribution and Sale. Determine if the firm is in compliance with 9 CFR 104.

f. Check U.S. Veterinary Biological Product Permits for Research and Evaluation and any permits for the importation or transportation of organisms or vectors issued to the licensee under 9 CFR 122, and compare with information on file at CVB. Ask for any additional permits the firm may have. Audit the firm's records for compliance with special requirements listed on the permits and with the regulations covering importation for research and evaluation. Check to determine if any of the permits have expired.

2. *Observations*:

a. Note the location of buildings and equipment used to produce, test, and store products to be sure that all premises are properly identified on the establishment license. Note any change in ownership, location, or operation of the establishment.

b. Verify that every product observed in production or testing on the licensed premises has a license or permit.

c. Check for compliance with special requirements of permits to import product for distribution and sale.

d. Inspect facilities where research material imported under permit is handled, and the conditions for handling this material, to be sure they meet requirements. Check for any other imported biologics on the licensed premises. Biologics exported from the United States may only be returned under a permit for research and evaluation.

B. Personnel

1. *Audits*:

a. Compare the firm's APHIS Form 2007 file with information on file at CVB for changes in key personnel. Check for deletions, additions, or job changes. Ask the official in charge to certify that the information on file at CVB is correct. Confirm the names of the official liaison and alternates.

b. Review the firm's system for keeping the APHIS Form 2007 file up to date. Identify the person responsible for making periodic reviews of the 2007 file.

c. Request a current copy of the firm’s organization chart or obtain the information necessary to allow you to establish official lines of responsibility within the firm. Check the relationships between production, testing, and marketing.

d. Determine if job titles accurately reflect job responsibilities.

e. Determine who supervises the care and welfare of animals, and which veterinarian determines the health of admitted animals.

2. *Observations:*

a. Observe if employees in key positions have APHIS Form 2007's on file at CVB. Observe if employees follow lines of responsibility as shown on the organizational chart or as explained by management.

b. Observe operations to determine if employees, in general, are adequately trained and supervised so as to be competent in good laboratory techniques. Be aware of personnel health conditions that might affect the product.

c. Notice if the number of employees is adequate, if they are observing in-house rules, and their general attitude toward their work.

C. Facilities

1. *Audits:*

a. Inspect all the premises and compare with the facility documents.

b. When comparing facilities with the filed drawings, look for evidence of unreported remodeling, new major equipment, relocated key items, and other discrepancies.

c. Check that legends showing special-use facilities (such as a public diagnostic clinic, separate and apart research areas, export-only products, pharmaceutics production, and FDA Export Reform and Enhancement Act production) are correct. Determine the location and adequacy of isolation facilities for incoming animals, if required.

2. *Observations:*

a. Verify that the actual use of production and testing rooms is as reported in the legends. Evaluate this use for any possible adverse effect on the product.

b. Observe the material, construction, and finish of all areas related to the production of biological products or ingredients of biological products. Verify that these areas may be readily and thoroughly cleaned.

c. Verify that the lights, ventilation systems, heating and cooling systems, hot and cold water supplies, and drainage systems are adequate and functioning.

d. Observe the arrangement and construction of the facilities. Determine if this arrangement and construction provide adequate and appropriate isolation for each product to prevent cross-contamination from other products.

e. Observe traffic patterns through the production area. Check enforcement of movement restrictions. A restricted area should be posted.

f. Evaluate the adequacy of the available space.

g. Verify that dressing rooms, toilets, and lavatories are appropriately placed, sufficient in number, and separated from production. Soap, towels, and hot water should be available.

D. Equipment

1. *Audits:*

a. Identify the automatically controlled equipment, environmental rooms, and other specialized equipment used in production, testing, and storage of product. Check that the location of this equipment matches the blueprint legends.

b. Review the records of operation of major specialized equipment, and determine if the equipment is functioning properly and recordkeeping is in compliance.

c. Determine what validation system is used and what records are kept by the firm to ensure that automatically controlled equipment is operating properly (see 9 CFR 109.1 and 109.2). If the firm has an exemption from having automatic recorders on sterilizers, determine if the records kept meet the provisions of 9 CFR 109.2.

2. *Observations:*

a. Check for major specialized equipment or environmental rooms not listed on the blueprint legend, and determine if they are being used in production, testing, or storage of product. Determine compliance.

b. Observe the operation of automatically controlled equipment and environmental rooms, and determine if they are being operated properly by the firm.

c. Note if each item of major equipment is uniquely marked so it may be identified in the records.

d. Check that all equipment is being sterilized according to 9 CFR 109.1 or has the appropriate exemption. Determine if equipment exempted under 9 CFR 109.2 is being adequately sterilized.

E. Sanitation

1. *Audits:*

a. Audit the firm's records to ensure that sanitizing is done at the appropriate time and place, and with the appropriate chemicals, as specified in the facility's blueprint legends.

b. Determine if the chemicals used for sanitation are appropriate for the microorganisms in each room.

2. *Observations:*

a. Notice if the outside premises are properly drained, are clean and orderly, and are free from accumulated trash or construction debris. No nuisance is allowed.

b. Note whether a conscientious effort is being made to control vermin, especially in animal quarters.

c. Check waste disposal methods to see if they are in accordance with VS Memorandum 800.56.

d. Check the inside premises for clutter. Check for accumulation of unnecessary materials, particularly in halls, production rooms, and coolers.

e. Notice whether all personnel, including maintenance people who enter production areas, are wearing appropriate clothing. Note if special clothing requirement areas are posted and requirements enforced.

f. Check for unsanitary practices by employees.

F. Establishments and/or Products Pending Licensure

1. *Audits:*

a. Examine records to confirm that the firm has obtained permission from LPD for any research that is conducted in production facilities, and that the firm has complied with any special requirements that were established.

b. Verify that the Master Seed is adequately identified and accounted for.

c. Check records for proper disposal of animals used in the preparation or testing of experimental products.

d. Differentiate between research being conducted using micoorganisms related to currently licensed products and work with new microorganisms not related to licensed products. Complete records are required for both, but fewer restrictions may be required for microorganisms related to currently licensed products.

e. Review field trial records for compliance with special restrictions and requirements. Determine the response rate of all participants. Were all the responses reported to LPD? Do the detailed records support the summaries sent to LPD?

f. For microorganisms related to licensed product but not approved for use in the production of licensed product: Check the firm's records for permission to maintain these microorganisms in the licensed establishment, for methods of maintenance, and for security procedures.

g. Review the minutes of Institutional Biosafety Committee meetings. Determine if appropriate members have been appointed. Determine if all biotechnology work and especially recombinant product work are being addressed and if appropriate policy and procedures have been established.

h. Determine if prelicensing serials were prepared in production facilities and tested on licensed premises.

2. *Observations:*

a. Determine if the separation of personnel, supplies, and equipment between research and production is adequate.

b. Observe the in-house controls on movement of personnel, supplies, and equipment and the airflow control between research, production, and testing areas.

c. Check for production-related testing in research areas.

d. Check methods for disposing of research material.

e. Observe specific research or prelicensing activities as requested by LPD.

f. Observe if employees are following biosafety policies.

g. Determine if biosafety policies are adequate.

G. Seeds and Cells

1. *Audits:*

a. List the bacterial and viral Master Seeds and Master Cell Stocks that are examined during the inspection, noting which were checked by observation, audit of records, or both. Note the seeds and cell stocks to which the Master Seed concept applies (9 CFR 113.8).

b. Check the records of each Master Seed and Master Cell Stock at each passage level for accountability and identification, tracing them from acquisition to production of serials. Be sure that records are complete. Note which tests to check later.

c. Determine if the Master Seeds and Master Cell Stocks being used in production agree with those listed in the corresponding Outlines of Production.

d. Determine if the licensee's system of identification is adequate to ensure that the proper Master Seed or Master Cell Stock has been used at the proper passage level in production. Verify that the Master Seeds, Working Seeds, Production Seeds, and Master Cell Stocks used in producing the product serial each have the same identity as those used in developing prelicense testing data. Also verify that the passage levels of the Master Seeds, Working Seeds, Production Seeds, and Master Cell Stocks used in producing the product serial are all acceptable based on the corresponding passage levels used in developing the prelicense testing data.

e. Determine where Master Seeds and Master Cell Stocks are maintained, handled, and produced. These materials have very specific requirements, which should be consistent with information in the blueprint legends.

f. Review records of Master Cell Stocks for batches of primary cells to determine their source, if the source animal was free of disease, and if acquisition was according to the regulations. Determine if batches of primary cells have been adequately tested.

g. Review Master Seed production and testing records. Review immunogenicity test and repeat immunogenicity test records. Determine if the bench records for each serial of product are complete and clearly trace to the Master Seed. Determine if required repeat immunogenicity tests have been done.

h. Review bench records or other data files from field trials of new products. Determine if summaries of the data correctly reflect all the field reports.

2. *Observations:*

a. Observe any production or testing procedures in progress for compliance with the Outline of Production or regulations. Note if the seeds are checked regularly for virulence, how they are maintained, how frequently they are passed, how they are stored, how much current inventory, etc.

b. Determine where Master Seed, Working Seed, and Production Seed are prepared. Only Master Seed may be prepared in separate and apart researchfacilities; Working Seed and Production Seed must be prepared on licensed premises in acceptable facilities.

c. Observe methods of maintenance, storage, and inventory of Master Seeds and Master Cell Stocks.

d. Check if there are separate storage facilities for virulent or dangerous microorganisms.

H. Production (through batching)

1. *Audits:*

a. List serials and production lots examined, noting which were checked by observation or record audit or both.

b. Review records of preselected production procedures for accountability and identification by tracing serials and production lots from raw ingredients to filling. Check that records are complete and that each major step is listed in the Outline of Production. If recordkeeping deficiencies are found, determine if they apply only to that serial or lot, or if they are consistent deficiencies for that product, group of products, or all products.

c. Determine if the serial or production lot has been prepared according to the version of the Outline of Production in effect when the lot was prepared; compare the date of production with the date on the outline used for reference. Check to see that each step listed in the outline is shown in the records. If deviations from the outline are noted, determine if they apply only to that serial or lot, that product, a group of products, or all products.

d. Determine if the manufacturer's recordkeeping system provides for the unique identification of each ingredient and if safeguards are in place to prevent errors in the preparation of the product.

e. Determine how serial numbers are assigned and what system is used. Ask the firm to update CVB if necessary.

f. Determine how annual outline reviews are done and by whom.

2. *Observations:*

a. Check any production procedure in progress for compliance with the most recent Outline of Production and blueprint legends.

b. Determine if the identity of in-process material is maintained. Note the manner of identification used and the consistency of its use, e.g., color coding, lot numbers, product name.

c. Observe whether proper laboratory techniques and sterile practices are followed by laboratory personnel where required.

d. Observe the preparation of equipment and media and other ancillary procedures in the service area for compliance with applicable special outlines.

e. Note any production procedures that differ from the Outline of Production, and evaluate the effect on the product. Even though the procedures may be within limits of acceptable laboratory practice or are intended to improve the product, variations are not allowed unless the outline is changed to reflect the variations. Determine if approved outlines are available to, and used by, line supervisors.

f. Look for any production procedures that may adversely affect the product.

I. Final Production (filling through packaging)

1. *Audits:*

a. Check filling records for recorded losses or gains, fill checks, and filling problems. Determine the firm's standard fill range and the maximum-minimum range for each fill size. Determine how over-filled or under-filled vials are handled and if the firm has a written policy covering this.

b. Determine the lyophilization requirements for each product. Review lyophilization records of selected serials for compliance and recordkeeping practices. Determine if temperature probe readings are identified on the recording charts.

c. Determine if all reprocessing was authorized, i.e., if further procedures were conducted on serials of liquid product after bulking and identification (other than filling and labeling) only when provided in the Outline of Production or when authorized by CVB.

d. Check records of controlled freezing to determine if procedures follow the Outline of Production for products where this is critical, such as Marek's Disease Vaccine.

e. Determine if losses incurred through breakage, loss of vacuum, etc., are noted in the serial records.

f. Determine if the firm attaches copies of the container label, the carton label, and the enclosure to the serial record.

2. *Observations:*

a. Observe and evaluate actual filling procedures, including aseptic technique, fill checks, proper mixing during fill, and maintenance of concurrent records. Determine if employees know the fill limits and how to handle unacceptably filled vials. Observe if fill limits are posted.

b. Check lyophilization procedures. Note stoppering devices. Note if different container sizes are mixed in one lyophilizer and if temperature varies on different shelves. Determine if placement of probes is adequate.

c. Note in-house procedures for vial and label inspection, sampling, identification of unlabeled vials, and how product is controlled until released.

d. Check handling of diluent, how and where it is stored, and how it is accounted for.

e. Check freezing procedures. Note the time interval from filling to start of freezing and the rate at which product temperature is lowered.

f. Observe several selected serials for product uniformity, color, volume, texture, opacity, labeling, packaging, serial number readability, and expiration date. Check Markem or silk screen labels to ensure they have not rubbed off and are legible.

g. Determine if products other than biologics are filled, packaged, or labeled on the licensed premises. Determine if adequate separation of licensed serials of product and non-licensed product is maintained during filling, packaging, and labeling.

h. Observe how long serials are out of the cooler during finishing procedures. Check if observed time is routine or an exception. Determine if this time may be detrimental to the product.

J. Labels

1. *Audits:*

a. Check the files of the firm's label controller for inactive, superseded, or obsolete labels.

b. Check labels for which there are special requirements in 9 CFR 112. Determine if these labels are in compliance.

c. Determine who assigns expiration dates and how it is done.

d. Determine how the label control person knows when a new label has been approved.

e. Check the label stock against the label file for accuracy. Check stock labels for color, style, printing, etc., and determine if there is any distinct difference from approved labels. Determine if stamped copies of approved labels are readily available to the person approving new label stock.

f. Check that the firm maintains accountability for all labels printed for use on licensed products. Check inventory records, and compare with actual inventories. How does the firm account for labels that are damaged or destroyed? Determine how the firm accounts for roll labels and if actual inventories are made by the firm.

2. *Observations:*

a. Check that labels are not left unattended where they could be pilfered or inadvertently used on the wrong product. Determine if unused imprinted roll labels are voided at the end of the labeling run.

b. Check security of labels in storage. Remember to check cartons, enclosures, and bottles that have been labeled prior to use.

c. Observe by whom and when imprinted serial numbers and expiration dates are inspected.

K. Testing

1. *Audits:*

a. For each test, list the product name, the serial or lot number, and whether the test was reviewed by examining records or by observation. Give special attention to tests that are not routinely confirmed by CVB Laboratory.

b. Records of testing done as required by the Outline of Production or regulations must show when observations are made and must be authenticated by the individual making the observations. Evaluate records for evidence of falsification. Review records of selected tests of ingredients, bulk lots, serials, Master Seeds, Master Cell Stocks, and diluents for compliance.

c. Note if tests contain the proper controls and if critical components, reagents, and equipment are monitored for quality before and/or during the test.

d. Make sure that all tests summarized on APHIS Form 2008 reports are supported by daily records.

e. Review any tests conducted by the firm that are not reported on the APHIS Form 2008. Determine whether or not these results indicate that the product may require special attention.

f. Evaluate whether retests are conducted according to regulations and/or the Outline of Production.

g. Check to see that the blueprint legend lists those microorganisms that are not named in the Outline of Production but that are necessary for testing purposes.

2. *Observations:*

a. Observe testing procedures to determine if they are in compliance with the Outline of Production and the regulations.

b. Observe testing procedures to determine if the firm is using proper laboratory technique along with proper recordkeeping.

c. Observe if proper testing controls are used.

L. Animals

1. *Audits:*

a. Determine if the firm is a registered research facility or a licensed animal dealer under the Animal Welfare Act. Record the registration or license numbers for reference. Review the last inspection report to see if there were any deficiencies. Determine if they have been corrected.

b. For animals used in production and testing, check procurement and test records for completeness, for accuracy, and for compliance with requirements in the Outline of Production and Animal Welfare regulations. Where required, ensure that proper health certificates have been issued and filed, e.g., equine infectious anemia testing records for horses used in production or testing.

c. Check the completeness of records for animals used in production or testing, and examine these records when inspecting according to the production and testing categories listed in this memorandum.

d. Determine if the firm keeps accurate records to identify animals and trace their final disposition. Certain animals must be quarantined before being removed from the premises and when moved must be accompanied by the appropriate forms.

2. *Observations:*

a. Check for compliance with requirements of the Animal Welfare Act. Animals not subject to the Act should also be cared for in the spirit of the Act. Report items needing immediate attention to the Animal Care Sector Supervisor at once.

b. Note whether animals are adequately identified.

c. Determine if a firm has post mortem facilities for animals used for production and test purposes.

d. Determine if the admitting veterinarian examines the animals before admittance or in a separate quarantine area on premises. Note if another employee examines the animals for the veterinarian.

e. Determine whether there is any preconditioning or treatment of animals that might adversely affect testing or production.

M. Distribution

1. *Audits:*

a. Evaluate the method of reconciling estimated and actual inventories.

b. Determine whether distribution records are adequate for inventory control.

c. Determine if the firm's records are such that the firm could carry out a total stop sale or recall down to user level should it become necessary.

d. Review documentation of any recent product recall or stop sale. Determine if the actions taken were appropriate and in accord with APHIS policy and guidelines (VS Memo 800.57).

e. Review the firm’s recall/stop sale policy to be sure that it is in accord with APHIS requirements.

2. *Observations:*

a. Evaluate the physical system of control and identification on pre- and post-release serials. The system should prevent inadvertent distribution of unreleased serials.

b. Review the release system with the firm to ensure adequate documentation and control. Verify who is designated to receive releases from Inspection and Compliance.

c. Compare the marketable inventory as reported on APHIS Form 2008 with the actual inventory. Record any significant changes in inventory.

d. Check if cooler space is adequate for licensed products at the normal level of production.

e. Observe for returned goods on premises. Determine how these goods are handled and disposed of. Check recordkeeping on returned goods.

N. Miscellaneous

1. *Audits:*

a. Discuss the firm's consumer complaints with the responsible official. Review the complaint files as indicated in CVB files or as required by license provisions.

b. Ensure that only authorized samplers sign the APHIS Form 2020. Arrange to train new and current samplers as necessary. Verify the list of authorized samplers.

c. Verify that products found unsatisfactory by the firm were destroyed and reported destroyed on an APHIS Form 2008.

d. Check the blueprint legends for notation of storage of reserve samples.

2. *Observations:*

a. Inspect storage areas to verify that products reported destroyed by the firm are not still being retained by the firm.

b. Inspect the quarantine area for separation and security.

c. Observe that only authorized samplers are selecting samples for APHIS testing.

d. Review sampling techniques. Be sure samples collected are representative. Check the methods of authentication and modify them if necessary. Check the method of packing samples for shipment.

e. Review APHIS Form 2020 preparation with the sampler. Countersign the APHIS Form 2020, and request testing according to the Inspection and Compliance Biologics Program Manual.

f. Check reserve samples for proper authentication and security.

g. Check that products "to be destroyed under APHIS supervision" have been properly quarantined. Observe the destruction of these products and report it on APHIS Form 2045. Check the inventory and accounting of any samples retained from unsatisfactory serials.

/s/ Karen A. James for

Alfonso Torres
Deputy Administrator
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